Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis

de Vries, Annemarie C.; Besselink, Marc G. H.; Buskens, Erik; Ridwan, Ben U.; Schipper, Maria; van Erpecum, Karel J.; Gooszen, Hein G.

Published in:
Pancreatology

DOI:
10.1159/000108971

Publication date:
2007

Rapid Communication

Pancreatology

Pancreatology 2007;7:531–538
DOI: 10.1159/000108971

Received: August 7, 2006
Accepted after revision: May 20, 2007
Published online: September 27, 2007

Randomized Controlled Trials of Antibiotic Prophylaxis in Severe Acute Pancreatitis: Relationship between Methodological Quality and Outcome

Annemarie C. de Vries[a] Marc G.H. Besselink[a] Erik Buskens[b] Ben U. Ridwan[c]
Maria Schipper[d] Karel J. van Erpecum[a] Hein G. Gooszen[a]

[a]Gastrointestinal Research Unit, Departments of Gastroenterology and Surgery, [b]Julius Center for Health Sciences and Primary Care, [c]Department of Microbiology, University Medical Center Utrecht, and [d]Centre for Biostatistics, Utrecht University, Utrecht, The Netherlands

Key Words
Pancreatitis · Antibiotic prophylaxis · Methodology, quality of · Meta-analysis · Necrotizing pancreatitis · Necrosis

Abstract
Aim: To evaluate the methodological quality of randomized controlled trials (RCTs) of systemic antibiotic prophylaxis in severe acute pancreatitis in relation to outcome. ***Methods:*** The MEDLINE, EMBASE and Cochrane databases were searched for RCTs that studied the effectiveness of systemic antibiotic prophylaxis in severe acute pancreatitis. A meta-analysis was performed with a random effects model. Methodological quality was quantified by a previously published scoring system (range 0–17 points). ***Results:*** Six studies, with a total of 397 participants, obtained a methodological score of at least 5 points and were included. Systemic antibiotic prophylaxis had no significant effect on infection of pancreatic necrosis (absolute risk reduction (ARR) 0.055; 95% CI −0.084 to 0.194) and mortality (ARR 0.058, 95% CI −0.017 to 0.134). Spearman correlation showed an inverse association between methodological quality and ARR for mortality (correlation coefficient −0.841, p = 0.036). ***Conclusions:*** The inverse relationship between methodological quality and impact of antibiotic prophylaxis on mortality emphasizes the importance of high-quality RCTs. At present, adequate evidence for the routine use of antibiotic prophylaxis in severe acute pancreatitis is lacking.

Part of this work was presented at the 2005 United European Gastroenterology Week (UEGW) in Copenhagen, Denmark, and published in abstract form in Gut 2005;54(suppl VII):A38–A39.

Introduction

Acute pancreatitis has an uncomplicated course in the majority of patients. However, approximately one fifth of patients will develop severe acute pancreatitis [1]. The majority of patients with severe acute pancreatitis suffer from complications, with an overall mortality of up to 30% [2]. Mortality is largely related to multi-organ failure early after the onset of pancreatitis and secondary infection of pancreatic necrosis by enteric bacteria during a second hit of the systemic inflammatory response syndrome [1, 2]. Systemic antibiotic prophylaxis has been

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1424–3903/07/0076–0531$23.50/0

Accessible online at:
www.karger.com/pan

H.G. Gooszen, MD, PhD
Department of Surgery, University Medical Center Utrecht, HP G04.228
PO Box 85500, NL–3508 GA Utrecht (The Netherlands)
Tel. +31 30 250 8074, Fax +31 30 254 1944
E-Mail h.gooszen@umcutrecht.nl and m.besselink@umcutrecht.nl

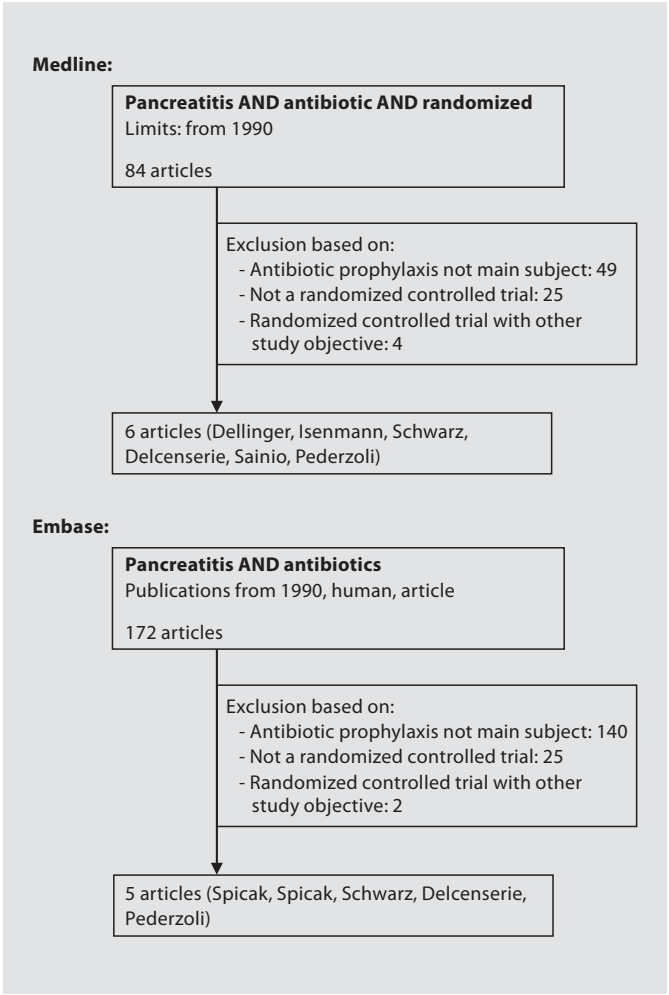

Fig. 1. Search strategy.

suggested as a strategy to prevent infection of pancreatic necrosis and consequently reduce mortality. Several randomized controlled trials (RCTs) have been performed to evaluate the efficacy of this strategy.

Although the results of these trials are conflicting, various guidelines [3, 4] and meta-analyses [5, 6] advocate the use of antibiotic prophylaxis in severe acute pancreatitis. However, these recommendations were published before the results of the first placebo-controlled RCT became available, which failed to demonstrate a beneficial effect of systemic antibiotic prophylaxis [7]. Nevertheless, two recent meta-analyses both including this trial still came to conflicting results [8, 9]. At present, there is no international consensus on the use of antibiotic prophylaxis in severe acute pancreatitis.

One of the main reasons for the lack of consensus is the frequently criticized methodological quality of the published RCTs [10]. The quality of these trials has never been systematically assessed. Recently, a scoring system was published that provides a quantitative measure of the methodological quality of RCTs [11]. We aimed to evaluate the evidence for routine administration of systemic antibiotic prophylaxis in patients with severe acute pancreatitis through both assessment of the methodological quality of the published RCTs and subsequent meta-analysis.

Methods

The MEDLINE, EMBASE and Cochrane databases were searched for studies on intravenous antibiotic prophylaxis published since 1990 using the search strategy shown in figure 1. Studies which compared the effectiveness of different antibiotic regimes or the effectiveness of different administration routes were excluded. There were no language restrictions, non-English manuscripts were translated.

Studies on selective decontamination of the digestive tract (SDD) were not included in the present analysis as they focus on a different prophylactic mechanism. SDD aims at preventing bacterial translocation from the gut prior to infection, whereas systemic antibiotic prophylaxis aims to diminish potential hematogenous spread of bacteria after translocation has occurred and/or to treat infection of (peri-)pancreatic necrosis.

The methodological quality of the retrieved RCTs was assessed using the previously published scoring system, which was adapted to the situation in severe acute pancreatitis in accordance with the revised CONSORT statement [12]. The following items were added to the scoring system: antibiotic intervention, method of feeding and participant flow. Three main items (population, intervention and participant flow), subdivided into eight criteria were scored. Zero, one or two points were given for each of the eight criteria (table 1).

Since the participant flow item is not subdivided into further criteria, a third point could be obtained for participant flow in order to weigh the items more equally in the final score. As a result, the maximum score for study quality was 17 points (table 1). Three researchers independently reviewed all studies (A.C.d.V., M.G.H.B., C.I.B.v.d.K.). In case of discrepant judgments a consensus reading followed. In order to include only studies of sufficient methodological quality in further analysis, in accordance with the study by van Nieuwenhoven et al. [11], a cutoff methodological score of 5 points was used.

Subsequently, meta-analysis of the trials was performed with a random effects model, thereby modeling the inter-study variance to estimate the overall effect of systemic antibiotic prophylaxis in severe acute pancreatitis.

The relation between the methodological quality of the studies and reported outcomes on infection of pancreatic necrosis and mortality was evaluated with a Spearman correlation coefficient, accounting for within-study variances. Significance was taken at $p < 0.05$.

Results

From 256 articles screened (fig. 1), 8 RCTs fulfilled the inclusion criteria [7, 13–19]. Two Czech trials were translated into English [17, 18]. The study of Nordback et al. [20] was excluded as antibiotic prophylaxis was used in both arms of the study.

Methodological Quality

The methodological quality score varied from 2 points for Spicak et al. [17] to 15 points for Isenmann et al. [7] and Dellinger et al. [19] (table 2). Both Czech trials [17, 18] scored less than 5 points and were consequently excluded (table 3).

Patient Characteristics

According to the methodological quality assessment, only Isenmann et al. [7] randomized patients into highly comparable groups. In most studies various baseline characteristics were not reported. Pederzoli et al. [14] included significantly more patients with more than 50% pancreatic necrosis in the antibiotic group.

Blinding

The studies of Isenmann et al. [7] and Dellinger et al. [19] were the only ones with a double-blind placebo-controlled design. Delcenserie et al. [13] and Schwarz et al. [16] did not clearly define the difference between 'antibiotic prophylaxis' and 'antibiotics on demand', possibly introducing bias.

Method of Feeding

The association of enteral feeding with a significantly lower incidence of infections has clearly been demonstrated [21]. Three studies [7, 15, 16], including the placebo-controlled trial from Isenmann et al. [7], did not state the method of feeding.

Participant Flow

Isenmann et al. [7] and Dellinger et al. [19] described the participant flow explicitly; the other trials did not mention the loss to follow-up and whether an intention-to-treat analysis was performed.

Meta-Analysis

The 6 RCTs with a methodological quality score of at least 5 points were included in the meta-analysis [7, 13–16, 19]. In total, 203 patients received antibiotic prophylaxis; 194 patients were included in the control group. For the individual studies the absolute risk reduction (ARR)

Table 1. Criteria for assessment of methodological quality

Score	Criteria
Population	
Patient selection	
2	Consecutive eligible consenting patients or random series
1	Attempt made to enroll as such, with failure due to reasons explicitly outlined
0	Selected patients (not consecutive or random) or not described
Patient characteristics	
2	Groups comparable on ≥7 characteristics
1	Groups comparable on 4–6 characteristics
0	Groups comparable on ≤3 characteristics
	Age (mean differs by <10%)
	Sex (proportion of men in each group differs by <10%)
	Ranson score (median differs by <1 point)
	Mean maximum C-reactive protein in first 48 h (mean differs by <10%)
	Pancreatic necrosis presence (proportion of patients differs by <10%)
	>30% pancreatic necrosis (proportion of patients differs by <10%)
	Etiology (mean proportions differ by <10%)
	Time (in days) between inclusion and onset of symptoms (mean differs by <10%)
Intervention	
Allocation sequence	
2	Computerized generated allocation, random number table
1	No more information
0	Quasi-randomization (date, etc.)
Concealment of allocation	
2	Non-manipulable (call to data center, masked drug packages)
1	Potentially manipulable (sealed envelope, computer-generated random number table) or randomization stated with no further information
0	Open label
Blinding	
2	Double-blind
1	Blinding of physicians to allocation
0	Potentially unblinded, unblinded, or cannot tell
Description of antibiotic intervention	
2	Indications for antibiotic crossover in control group described
1	Indications for antibiotic crossover stated afterwards
0	Indications for antibiotic crossover in control group not described
Description of method of feeding	
2	Method of feeding in both groups described
1	Method of feeding only described in antibiotic or control group
0	Method of feeding not described
Participant flow	
3	<10% loss to follow-up; reasons for loss to follow-up outlined; intention-to-treat analysis
2	Two of above items
1	One of above items
0	Participant flow not described

Table 2. Methodological quality score

	Methodological quality score	Population		Intervention					Participant flow
		patient selection	patient characteristics	allocation sequence	concealment of allocation	blinding	description of antibiotic intervention	feeding protocol	
Pederzoli et al. [14]	10	2	1	2	1	0	2	2	0
Sainio et al. [15]	8	2	1	2	1	0	2	0	0
Delcenserie et al. [13]	8	2	1	2	1	0	0	2	0
Schwarz et al. [16]	5	2	1	1	1	0	0	0	0
Spicak et al. [17]	2	2	0	0	0	0	0	0	0
Spicak et al. [18]	4	2	0	1	1	0	0	0	0
Isenmann et al. [7]	15	2	2	2	2	2	2	0	3
Dellinger et al. [19]	15	2	1	2	2	2	1	2	3

Table 3. Characteristics of the randomized controlled trials

	Year	n	Setting	Domain				Intravenous antibiotic(s)
				inclusion criteria	etiology	prognostic score, mean Ranson score	pancreatic necrosis on CT	
Pederzoli et al. [14]	1993	74	6 hospitals Italy	PN on CECT	Biliary 50% Alcohol 32% Other 18%	3.7	>30% PN in 53% of patients >50% PN in 22% of patients	Imipenem
Sainio et al. [15]	1995	60	1 university hospital Finland	CRP >120 mg/l and low contrast enhancement on CECT or extrapancreatic score >4 on CT	Alcohol 100%	5.5	>33.3% PN in 80% of patients	Cefuroxime
Delcenserie et al. [13]	1996	23	1 hospital France	Two or more fluid collections on CT	Alcohol 100%	2.3	–	Ceftazidime, amikacine, metronidazole
Schwarz et al. [16]	1997	26	1 university hospital Germany	PN on CECT	Biliary 42% Alcohol 54% Other 4%	4.8	mean 40% PN	Ofloxacin, metronidazole
Isenmann et al. [7]	2004	114	19 hospitals Germany	CRP >150 mg/l and/or PN on CECT	Biliary 19% Alcohol 58% Other 23%	2.3	>30% PN in 21% of patients	Ciprofloxacin, metronidazole
Dellinger et al. [19]	2007	100	32 hospitals in North America and Europe	PN >30% on CECT or Balthazar grade E on CT with either CRP >120 mg/l or MOD score >2	Biliary 34% Alcohol 44% Other 22%	4.2	>30% PN in 57% of patients	Meropenem

PN = Pancreatic necrosis; CECT = contrast-enhanced computed tomography; CRP = C-reactive protein; MOD = multiple organ dysfunction.

for infection of pancreatic necrosis ranged from –0.077 to 0.333 and the relative risk reduction (RRR) from –46.2 to 87.8%. For mortality the ARR ranged from –0.02 to 0.2, the RRR from –10.5 to 80%. There was no overall significant reduction in infection of pancreatic necrosis, ARR 0.055 (95% confidence interval (CI) –0.084 to 0.194) and mortality, ARR 0.058 (95% CI –0.194 to 0.154; table 4; fig. 2, 3).

Methodological Quality in Relation to Study Outcome

The Spearman correlation coefficient showed no significant relationship between the methodological qual-

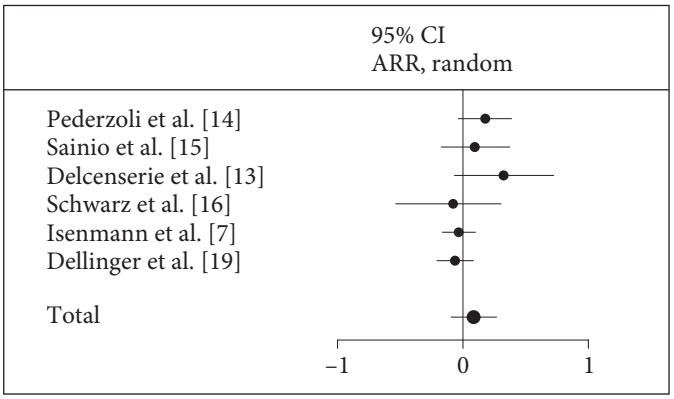

Fig. 2. Meta-analysis: absolute risk reduction (ARR) of infected pancreatic necrosis.

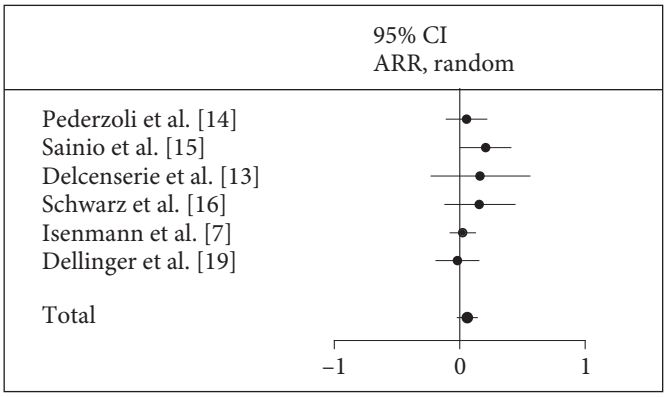

Fig. 3. Meta-analysis: absolute risk reduction (ARR) of mortality.

Table 4. Absolute (ARR) and relative risk reductions (RRR) of infected pancreatic necrosis and mortality

	AB group	Control group	ARR	95% CI	RRR	95% CI
Infected pancreatic necrosis						
Pederzoli et al. [14]	5/41	10/33	0.181	–0.031; 0.393	0.576 (57.6%)	–0.072; 0.832
Sainio et al. [15]	9/30[a]	12/30[a]	0.1	–0.175; 0.375	0.240 (24.0%)	–0.502; 0.615
Delcenserie et al. [13]	0/11	4/12[a]	0.333	–0.064; 0.731	0.878 (87.8%)	–1.008; 0.993
Schwarz et al. [16]	8/13	7/13	–0.077	–0.534; 0.380	–0.133 (–13.3%)	–1.159; 0.405
Isenmann et al. [7]	7/58	5/56	–0.031	–0.162; 0.099	–0.317 (–31.7%)	–2.721; 0.534
Dellinger et al. [19]	9/50	6/50	–0.060	–0.200; 0.080	–0.462 (–46.2%)	–2.664; 0.417
Total	38/203	44/194	0.055	–0.084; 0.194	0.101 (10.1%)	–0.430; 0.435
Mortality						
Pederzoli et al. [14]	3/41	4/33	0.048	–0.113; 0.210	0.370 (37.0%)	–1.361; 0.832
Sainio et al. [15]	1/30	7/30	0.2	–0.005; 0.405	0.800 (80.0%)	–0.074; 0.963
Delcenserie et al. [13]	1/11	3/12	0.159	–0.238; 0.556	0.536 (53.6%)	–1.657; 0.919
Schwarz et al. [16]	0/13	2/13	0.153	–0.128; 0.436	0.800 (80.0%)	–2.801; 0.989
Isenmann et al. [7]	3/58	4/56	0.020	–0.086; 0.125	0.249 (24.9%)	–1.895; 0.805
Dellinger et al. [19]	10/50	9/50	–0.020	–0.194; 0.154	–0.105 (–10.5%)	–1.428; 0.497
Total	18/203	29/194	0.058	–0.017; 0.134	0.301 (30.1%)	–0.403; 0.652

[a] Pancreatic abscess included.

ity of the trials and the reported risk of infected pancreatic necrosis (table 5). With the Spearman correlation coefficient, an inverse significant relationship between methodological score and the ARR (correlation coefficient –0.841, p = 0.036) and RRR for mortality (correlation coefficient–0.948, p = 0.004) was demonstrated (table 5; fig. 4).

Discussion

This study demonstrates that the study quality of the included RCTs was generally moderate. Interestingly, the effect of antibiotic prophylaxis on mortality seemed smaller in studies of higher methodological quality.

Strikingly, the findings in the study of van Nieuwenhoven et al. [11] regarding the methodological quality of

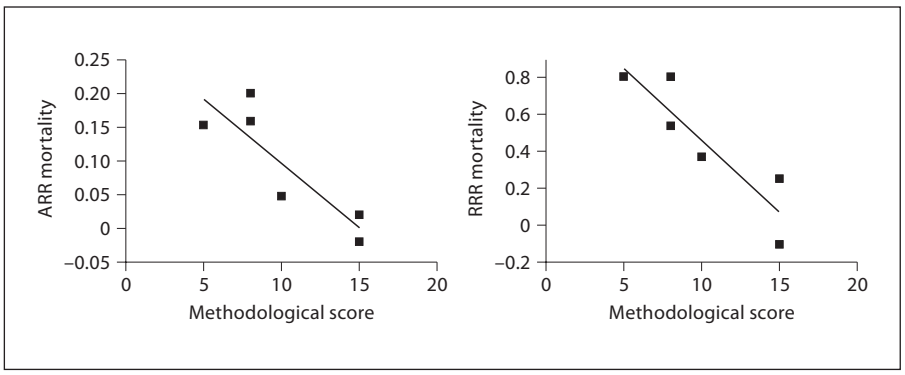

Fig. 4. Significant relationship between methodological quality scores and risk reduction of mortality. ARR = Absolute risk reduction; RRR = relative risk reduction.

Table 5. Association between methodological quality score and risk reduction of infection of pancreatic necrosis and mortality with linear regression analysis

	Correlation coefficient	p value
ARR infected necrosis	–0.438	0.385
RRR infected necrosis	–0.403	0.429
ARR mortality	–0.841	0.036
RRR mortality	–0.948	0.004

the studies on SDD in intensive care patients were similar to ours, i.e. an inverse relationship between methodological quality score and the benefit of antibiotic prophylaxis. An assessment of the methodological quality of studies based on the information in published articles could be influenced by flaws in reporting trials, i.e. something may not be reported although it was correctly performed. Obviously, it is impossible to correct for this factor. In our meta-analysis, trials were weighted regardless of the methodological score. At this moment, there are no guidelines on how to weigh studies of specific methodological quality when combining results in a meta-analysis.

The heterogeneity of studies included in a meta-analysis reduces the reliability in general [22]. Several factors could have influenced the outcome of the present meta-analysis. Firstly, two studies [13, 15] included only patients with alcohol-induced pancreatitis, whereas the other studies included patients regardless of the etiology of pancreatitis. There is controversy, however, about whether the etiology of pancreatitis influences mortality [23–26]. Secondly, it is plausible that inclusion of less ill patients and patients without pancreatic necrosis leads to underestimation of the effect of systemic antibiotics in patients with acute pancreatitis. However, the patients included in the study with the largest effect size of antibiotic prophylaxis on infection [13] had the lowest mean Ranson score of 2.3, predicting mild pancreatitis. Thirdly, only two studies were double-blind, placebo-controlled [7, 19]. In the other studies, the absence of blinding might have led to a higher prescription rate of antibiotics in the control group. The risk of early 'cross-over' (use of antibiotics in the control group) demands standardization of antibiotic indications, especially in studies without blinding. Total crossover rates were only reported in the studies by Sainio et al. [15] (77%), Isenmann et al. [7] (46%) and Dellinger et al. [19] (52%). Finally, the antibiotics used in the studies varied (table 3); one study with imipenem [14], one study with meropenem [19], two with cephalosporins [13, 15], and two with a combination of third-generation fluoroquinolones and metronidazole [7, 16]. This makes it difficult to compare the outcome, since it could be influenced by, amongst others, the level of penetration of the antibiotics in (necrotic) pancreatic tissue and the antimicrobial spectrum of the antibiotics [27–30].

Since the use of broad-spectrum antibiotic prophylaxis may lead to bacterial resistance [31], fungal infections [32], selective overgrowth of pathogens leading to, for instance, *Clostridium difficile* colitis [33] and increased costs [34], the balance between beneficial and harmful effects of antibiotic prophylaxis should clearly be in favor of antibiotics in order to justify their use. The current meta-analysis demonstrated no beneficial effects of antibiotic prophylaxis on the incidence of both infected pancreatic necrosis and mortality. Furthermore, in the RCT from Isenmann et al. [7], patients receiving antibiotic prophylaxis experienced a significant increase in infections with bacteria resistant to the prophylactic antibiotics administered.

Conclusion

Routine use of antibiotic prophylaxis in severe acute pancreatitis does not prevent infection of pancreatic necrosis and mortality. The generally moderate quality of the studies may have contributed to an overly enthusiastic opinion on the effect of antibiotic prophylaxis in patients with severe acute pancreatitis. At present, opinion-based medicine has taken over, resulting in widespread use of antibiotic prophylaxis in severe acute pancreatitis. The inverse relationship between methodological quality and the impact of antibiotic prophylaxis on mortality emphasizes the importance of high-quality RCTs.

Acknowledgements

The authors wish to thank C.I.B. van de Kraats, MD, for reviewing the studies and performing data extraction and P. Kohout, MD, for translating the Czech trials. M.G.H. Besselink is a MD-medical research trainee for the Netherlands Organization for Health Research and Development (ZonMw, grant No. 920-03-368).

References

1 Beger HG, Rau B, Mayer J, Pralle U: Natural course of acute pancreatitis. World J Surg 1997;21:130–135.
2 Working Party of the British Society of Gastroenterology; Association of Surgeons of Great Britain and Ireland; Pancreatic Society of Great Britain and Ireland; Association of Upper GI Surgeons of Great Britain and Ireland: UK guidelines for the management of acute pancreatitis. Gut 2005;54(suppl 3):iii1–iii9.
3 Toouli J, Brooke-Smith M, Bassi C, Carr-Locke D, Telford J, Freeny P, Imrie C, Tandon R: Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol 2002; 17(suppl 1):15–39.
4 Uhl W, Warshaw A, Imrie C, Bassi C, McKay CJ, Lankisch PG, Carter R, Di Magno E, Banks PA, Whitcomb DC, Dervenis C, Ulrich CD, Satake K, Ghaneh P, Hartwig W, Werner J, McEntee G, Neoptolemos JP, Buchler MW: IAP Guidelines for the Surgical Management of Acute Pancreatitis. Pancreatology 2002;2:565–573.
5 Golub R, Siddiqi F, Pohl D: Role of antibiotics in acute pancreatitis: a meta-analysis. J Gastrointest Surg 1998;2:496–503.
6 Sharma VK, Howden CW: Prophylactic antibiotic administration reduces sepsis and mortality in acute necrotizing pancreatitis: a meta-analysis. Pancreas 2001;22:28–31.
7 Isenmann R, Runzi M, Kron M, Kahl S, Kraus D, Jung N, Maier L, Malfertheiner P, Goebell H, Beger HG: Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology 2004; 126:997–1004.
8 Heinrich S, Schafer M, Rousson V, Clavien PA: Evidence-based treatment of acute pancreatitis: a look at established paradigms. Ann Surg 2006;243:154–168.
9 Mazaki T, Ishii Y, Takayama T: Meta-analysis of prophylactic antibiotic use in acute necrotizing pancreatitis. Br J Surg 2006;93: 674–684.
10 Brown A: Prophylactic antibiotic use in severe acute pancreatitis: hemlock, help, or hype? Gastroenterology 2004;126:1195–1198.
11 van Nieuwenhoven CA, Buskens E, van Tiel FH, Bonten MJ: Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. JAMA 2001;286:335–340.
12 Moher D, Schulz KF, Altman DG: The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357:1191–1194.
13 Delcenserie R, Yzet T, Ducroix JP: Prophylactic antibiotics in treatment of severe acute alcoholic pancreatitis. Pancreas 1996;13: 198–201.
14 Pederzoli P, Bassi C, Vesentini S: A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet 1993;176:480–483.
15 Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V, Haapiainen R, Schroder T, Kivilaakso E: Early antibiotic treatment in acute necrotising pancreatitis. Lancet 1995;346:663–667.
16 Schwarz M, Isenmann R, Meyer H, Beger HG: Antibiotic use in necrotizing pancreatitis. Results of a controlled study (in German). Dtsch Med Wochenschr 1997;122: 356–361.
17 Spicak J, Hubaczovai M, Antos F, Bairtovai J, Cech P, Kasalickyi M, Kostka R, Lata J, Leffler J, Zavoral M: Antibiotics in the treatment of acute pancreatitis – findings from a randomized multi-centre prospective study (in Czech). Cesk Slov Gastroenterol Hepatol 2002;56:183–189.
18 Spicak J, Hejtmainkovai S, Hubaczovai M, Antos F, Bairtovai J, Cech P, Kasalickyi M, Kosta R, Lata J, Leffler J, Solar S, Svoboda P, Zavoral M: Antibiotic prophylaxis of infectious complications of acute pancreatitis – the results of randomised study by meropenem (in Czech). Cesk Slov Gastroenterol Hepatol 2003;57:222–227.
19 Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, Imrie CW, Johnson CD, Knaebel HP, Laterre PF, Maravi-Poma E, Kissler JJ, Sanchez-Garcia M, Utzolino S: Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg 2007;245:674–683.
20 Nordback I, Sand J, Saaristo R, Paajanen H: Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis – a single-center randomized study. J Gastrointest Surg 2001;5:113–118.
21 Marik PE, Zaloga GP: Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. BMJ 2004; 328:1407.
22 Thompson SG: Why sources of heterogeneity in meta-analysis should be investigated. BMJ 1994;309:1351–1355.
23 Gullo L, Migliori M, Pezzilli R, Olah A, Farkas G, Levy P, Arvanitakis C, Lankisch P, Beger H: An update on recurrent acute pancreatitis: data from five European countries. Am J Gastroenterol 2002;97:1959–1962.
24 Lankisch PG, Burchard-Reckert S, Petersen M, Lehnick D, Schirren CA, Stockmann F, Kohler H: Etiology and age have only a limited influence on the course of acute pancreatitis. Pancreas 1996;13:344–349.

25 Pezzilli R, Billi P, Morselli-Labate AM: Severity of acute pancreatitis: relationship with etiology, sex and age. Hepatogastroenterology 1998;45:1859–1864.
26 Uhl W, Isenmann R, Curti G, Vogel R, Beger HG, Buchler MW: Influence of etiology on the course and outcome of acute pancreatitis. Pancreas 1996;13:335–343.
27 Bassi C, Pederzoli P, Vesentini S, Falconi M, Bonora A, Abbas H, Benini A, Bertazzoni EM: Behavior of antibiotics during human necrotizing pancreatitis. Antimicrob Agents Chemother 1994;38:830–836.
28 Bassi C: Infections in pancreatic inflammatory disease: clinical trials for antibiotic prophylaxis. Pancreatology 2001;1:210–212.
29 Cinar E, Ateskan U, Baysan A, Mas MR, Comert B, Yasar M, Ozyurt M, Yener N, Mas N, Ozkomur E, Altinatmaz K: Is late antibiotic prophylaxis effective in the prevention of secondary pancreatic infection? Pancreatology 2003;3:383–388.
30 Buchler M, Malfertheiner P, Friess H, Isenmann R, Vanek E, Grimm H, Schlegel P, Friess T, Beger HG: Human pancreatic tissue concentration of bactericidal antibiotics. Gastroenterology 1992;103:1902–1908.
31 De Waele JJ, Vogelaers D, Hoste E, Blot S, Colardyn F: Emergence of antibiotic resistance in infected pancreatic necrosis. Arch Surg 2004;139:1371–1375.
32 Isenmann R, Schwarz M, Rau B, Trautmann M, Schober W, Beger HG: Characteristics of infection with Candida species in patients with necrotizing pancreatitis. World J Surg 2002;26:372–376.
33 Wren SM, Ahmed N, Jamal A, Safadi BY: Preoperative oral antibiotics in colorectal surgery increase the rate of *Clostridium difficile* colitis. Arch Surg 2005;140:752–756.
34 Berild D, Ringertz SH, Lelek M, Fosse B: Antibiotic guidelines lead to reductions in the use and cost of antibiotics in a university hospital. Scand J Infect Dis 2001;33:63–67.